

Dichlorodiphenyldichloroethane Burden and Breast Cancer Risk: A Meta-Analysis of the Epidemiologic Evidence

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The relationship of dichlorodiphenyltrichloroethane (DDT) exposure and breast cancer risk has received increasing attention since the beginning of the 1990s. Contradicting published results regarding the relationship between body burden levels of *p,p'*-dichlorodiphenyldichloroethane (*p,p'*-DDE)—the main DDT metabolite—and breast cancer, we argue that such differences stem from methodologic differences among those studies. We performed a meta-analysis of 22 articles using DerSimonian and Laird's method for random effects models. The Q-statistic was used to identify heterogeneity in the outcome variable across studies. The gradient of *p,p'*-DDE exposure in epidemiologic studies was homogenized to serum lipid bases (nanograms per gram). The potential for publication bias was examined by means of the Begg's test. We discuss methodologic features of the studies in an attempt to reconcile the findings. The summary odds ratio (OR) for selected studies was 0.97 (95% confidence interval, 0.87–1.09) and the gradient of exposure ranged from 84.37 to 12,948 ng/g. No overall heterogeneity in the OR was observed ($\chi^2 = 27.93$; $df = 23$; $p = 0.218$). Neither the study design nor the lack of breast-feeding control or the type of biologic specimen used to measure *p,p'*-DDE levels were the causes of heterogeneity throughout the studies. Evidence for publication bias was not found ($p = 0.253$). Overall, these results should be regarded as a strong evidence to discard the putative relationship between *p,p'*-DDE and breast cancer risk. Nevertheless, the exposure to DDT during critical periods of human development—from conception to adolescence—and individual variations in metabolizing enzymes of DDT or its derivatives are still important areas to be researched in regard to breast cancer development in adulthood. **Key words:** breast cancer, DDT, epidemiology, evidence, meta-analysis. *Environ Health Perspect* 112:207–214 (2004). doi:10.1289/ehp.6492 available via <http://dx.doi.org/> [Online 22 October 2003]

The insecticide dichlorodiphenyltrichloroethane (DDT) was first synthesized in 1874 and reached worldwide use during the early 1960s to control malaria and some agricultural pests. In 1972 the use of DDT was banned in the United States, and by the beginning of the 1980s this chemical was prohibited in most developed countries. However in India, Indonesia, and Italy, DDT was still produced until 1990, and in Mexico DDT was in use until 1997 to control malaria (Turusov et al. 2002). The long persistence and environmental spreading exhibited by DDT and its metabolites, along with their estrogenic potential, are the main concerns regarding its potential role in the etiology of estrogen-related malignant tumors (Snedeker 2001).

In 1993, Wolff et al. (1993) first reported on the presumed positive association between *p,p'*-dichlorodiphenyldichloroethane (*p,p'*-DDE)—the main metabolite of DDT—and breast cancer, and subsequently the assessment of the body burden of DDT metabolites in relation to breast cancer risk received a lot of attention. During the last decade, results from several epidemiologic studies were published but most were unable to replicate the positive association between *p,p'*-DDE and breast cancer risk. Among other explanations for such negative results, some suggested—but never proved—that single studies lacked

an adequate gradient of exposure to *p,p'*-DDE among breast cancer cases and controls, and this flaw obscured the differences (Talbot et al. 1998). As demonstrated below, the gradient exposure in 22 published studies ranged from 84.37 to 12928.08 ng/g (Aronson et al. 2000; Dello Iacovo et al. 1999; Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Stellman et al. 2000; van't Veer et al. 1997; Wolff et al. 1993, 2000a, 2000b; Zheng et al. 1999, 2000), in sharp contrast to the narrower gradients achieved by most single studies.

Serum and adipose tissue were the human biologic matrices used to estimate *p,p'*-DDE body burden and its potential relationship with breast cancer risk. Circulating lipids influence blood levels of DDT metabolites (Phillips et al. 1989), yet approaches to this condition varied greatly in the published scientific literature. Some studies reported *p,p'*-DDE serum levels in lipid bases (Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000a, 2000b; Laden et al. 2001; López-Carrillo et al. 1997; Millikan et al. 2000; Romieu et al. 2000; Ward et al. 2000; Wolff et al. 2000a, 2000b; Zheng et al. 2000), whereas others performed

an indirect adjustment by fitting a cholesterol term in linear regression models (Dello Iacovo et al. 1999; Hunter et al. 1997; Moysich et al. 1998) and the rest only provided wet-based measurements (Krieger et al. 1994; Mendonca et al. 1999; Olaya-Contreras et al. 1998; Schecter et al. 1997; Wolff et al. 1993). This heterogeneity among biologic matrices and reported units of cumulative *p,p'*-DDE levels limited the ability to evaluate the gradient of *p,p'*-DDE body burden levels across the epidemiologic studies published so far.

In this article we aim to *a*) estimate the strength of the association between *p,p'*-DDE and breast cancer on the basis of published epidemiologic evidence; *b*) identify the gradient of exposure that was captured in the same epidemiologic studies; and *c*) discuss the consistency of published results in the context of their main methodologic features.

Materials and Methods

We searched for the epidemiologic evidence on *p,p'*-DDE and breast cancer risk in both the MEDLINE and PubMed databases (www.ncbi.nlm.nih.gov). A total of 35 analytic studies (Aronson et al. 2000; Bagga et al. 2000; Dello Iacovo et al. 1999; Demers et al. 2000; Dewailly et al. 1994; Dorgan et al. 1999; Duell et al. 2000; Falck et al. 1992; Güttes et al. 1998; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000a, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001a; Liljegren et al. 1998; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Olaya-Contreras et al. 1998; Romieu et al. 2000; Schecter et al. 1997; Stellman et al. 2000; Unger et al. 1982, 1984; van't Veer et al. 1997; Ward et al. 2000; Wassermann et al. 1976; Wolff et al. 1993, 2000a, 2000b; Zheng et al. 1999, 2000) that were published

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We thank M. Wolff and M. Cebrian for their support in the interlaboratory standardization of *p,p'*-DDE levels in biologic samples for the case-control study by López-Carrillo et al. We also thank R. Collado for editing the manuscript.

The authors declare they have no competing financial interests.

Received 2 June 2003; accepted 22 October 2003.

in English up to February 2001 were found using the following MeSH headings, key, and text words: breast cancer, organochlorines, pesticides. The articles identified were then reviewed to determine whether they met the following inclusion criteria for statistical analyses: to be epidemiologic cohort or case-control studies; to have enrolled at least 50 cases; to have reported measures of association and confidence intervals (CIs) for breast cancer risk; to have measured *p,p'*-DDE levels in biologic samples (serum or adipose tissue); and to have been published in journals listed by the Journal Citation Reports—Science Edition (JCR) (1999).

Under the former considerations, six articles were discarded because no measures of association were reported (Dewailly et al. 1994; Falck et al. 1992; Güttes et al. 1998; Unger et al. 1984, 1982; Wassermann et al. 1976), one more was eliminated because it lacked CIs (Ward et al. 2000), another article was excluded because the researchers evaluated survival instead of breast cancer risk (Hoyer et al. 2000a), another one did not measure *p,p'*-DDE levels in biologic samples (Duell et al. 2000), one was not published in a JCR journal (Olaya-Contreras et al. 1998), two reported on < 50 breast cancer cases (Liljegren et al. 1998; Schecter et al. 1997) and one study used a cross-sectional design (Bagga

et al. 2000). These 13 epidemiologic studies were discarded in this step and 22 were kept for further analyses (Aronson et al. 2000; Dello Iacovo et al. 1999; Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Stellman et al. 2000; van't Veer et al. 1997; Wolff et al. 1993, 2000a, 2000b; Zheng et al. 1999, 2000).

From each eligible report and using a pre-defined review form, two independent reviewers extracted the following methodologic information: name of the author, year and place of publication, epidemiologic design, type of controls and biologic specimens, confounding variables considered in the analysis, and the measure of association estimated for the highest versus lowest category of exposure along with the corresponding CI.

After their extraction, we entered relevant data into evidence tables. We then performed a meta-analysis using the method of the inverse of variance for fixed-effects models and the DerSimonian and Laird method for random-effects models. (DerSimonian and Laird 1986). Separate odds ratios (ORs) were used in the meta-analysis for one article that reported estimates from population-based and

hospital controls (Demers et al. 2000), and the same was done with estimates from one study in which serum samples were taken and analyzed for two different periods of time (Helzlsouer et al. 1999). The results are displayed as summary ORs and 95% CIs for the effect of *p,p'*-DDE on breast cancer, corresponding to the contrast of the highest versus the lowest level of *p,p'*-DDE exposure.

We plotted the outcomes for included studies for visual examination and performed meta-analysis regression using the Q-statistic to identify heterogeneity in the outcome variable across studies (Berkey et al. 1995; DerSimonian and Laird 1986). Potential sources of heterogeneity were evaluated, including the study design, control for breastfeeding and the kind of biologic specimen in which the DDT metabolites were measured. We assessed the potential for publication bias using a funnel plot in conjunction with the Begg's test, which is based on the fact that smaller studies tend to have larger effect size estimates and the publication bias induces a correlation between the effect estimates and their variances (Begg 1985, 1994).

To estimate the trend of *p,p'*-DDE body burden evaluated by the epidemiologic studies analyzed, we determined the crude mean *p,p'*-DDE levels among cases and controls reported by each study and homogenized

Table 1. Prospective epidemiologic studies (nested case-control) on *p,p'*-DDE and breast cancer risk.

Reference, location	Cases/controls (n)	Controls	Biologic specimen (year of collection)	Controlled variables ^a				<i>p,p'</i> -DDE ORs (95% CI)
				Age	Reproductive variables	History of breast cancer	Other variables	
Laden et al. 2001b 11 large states, USA	381/381	Free of cancer	Serum (1989–1990)	X	X	X	X ^b	High vs. low quintile 0.82 (0.49–1.37)
Wolff et al. 2000b New York City, USA	110/213	Free of disease	Serum (1985–1991)	X	X	X	X ^c	High vs. low quartile 1.30 (0.51–3.35)
Hoyer et al. 2000b Copenhagen, Denmark	240/477	Free of disease	Serum (1976–1983)	X	X Except breast-feeding	—	X ^d	High vs. low quartile 1.4 (0.7–2.8)
Dorgan et al. 1999 Columbia, Missouri, USA	105/207	Free of cancer except skin cancer	Serum (1977–1987)	X	—	—	X ^e	High vs. low quartile 0.8 (0.4–1.5)
Helzlsouer et al. 1999 Washington Co., Maryland, USA	235/235 105/105	Free of cancer except skin cancer	Serum (1974)	X	X	X	X ^f	High vs. low quintile 0.73 (0.40–1.32)
Hoyer et al. 1998 Copenhagen, Denmark	237/469	Free of breast cancer	Serum (1976)	X	X Except breast-feeding	—	X ^g	High vs. low quartile 0.88 (0.56–1.37)
Hunter et al. 1997 Boston, MA, USA	236/236	Free of cancer	Serum (1989–1990)	X	X	X	X ^h	High vs. low quintile 0.72 (0.37–1.40)
Krieger et al. 1994 California, USA	150/150	Free of cancer	Serum (1964–1971)	X	X Except breast-feeding	—	X ⁱ	High vs. low tertile 1.33 (0.68–2.62)
Wolff et al. 1993 New York City, USA	58/171	Free of cancer	Serum (1985–1991)	X	X	X	X ^j	High vs. low quintile 3.68 (1.01–13.5)

Abbreviations: BMI, body mass index; ln, natural logarithm.
^aIn design or analysis. ^bDate in which blood sample was returned, time of day that blood sample was obtained, fasting status at blood sampling and for postmenopausal hormone use, BMI at blood collection, history of benign breast disease. ^cNumber and dates of blood donations, day of menstrual cycle for premenopausal women, ln height, ln (BMI) –menopausal status at blood donation interaction. ^dVital statistics at time of diagnosis and weight. ^eYear of blood draw and history of benign disease at the time of diagnosis. ^fDate of blood donation and day of menstrual cycle, race, BMI at age 20 or current. ^gDate of examination and vital status at the time of diagnosis, weight, height, alcohol consumption, smoking, physical activity, income, marital status, and education. ^hSerum lipids, month in which the blood sample was returned, time of day that the blood sample was obtained, fasting status at blood sampling, postmenopausal hormone use, history of benign breast disease, BMI. ⁱDate of examination, length of follow-up after examination, race, date of joining the Kaiser Permanente Medical Care Program, year of multiphasic examination and BMI. ^jNumber and date of blood donation, if premenopausal women: day of menstrual cycle at the time of the first blood drawing.

them to serum *p,p'*-DDE levels in lipid bases (nanograms per gram) as follows: the arithmetic mean serum levels of *p,p'*-DDE in wet bases (nanograms per milliliter) were multiplied by a factor of 129.8 to convert them to the arithmetic mean of serum levels in lipid basis (nanograms per gram), and otherwise the arithmetic means of adipose tissue levels of *p,p'*-DDE were divided by a factor of 4.2 to estimate the corresponding serum levels in lipid basis (nanograms per gram) (López-Carrillo et al. 1999).

The percent of recovery of *p,p'*-DDE levels was not considered. Five articles did not provide mean values of *p,p'*-DDE and thus were not included (Dorgan et al. 1999; Hoyer et al. 1998, 2000b; Laden et al. 2001b; Stellman et al. 2000); also not included were two others that reported adjusted mean values of *p,p'*-DDE (Zheng et al. 1999, 2000) and three in which the *p,p'*-DDE levels were statistically modeled through the contents of triglycerides, serum, and total cholesterol (Dello Iacovo et al. 1999; Hunter et al. 1997; Moysich et al. 1998). Therefore, we included 12 studies in this step of the analysis. We estimated the trend of the mean *p,p'*-DDE body burden levels in nanograms per gram according to the year when the biologic samples were collected by linear regression.

To evaluate the gradient of *p,p'*-DDE body burden captured by studies of interest, we plotted the middle point of *p,p'*-DDE levels in nanograms per gram in serum (according to the methodology already described) for each category of exposure, against the corresponding ORs reported by 17 studies. We did not include two studies because no information on the magnitude of *p,p'*-DDE quartile distribution was provided (Hoyer et al. 1998, 2000b) and three studies in which *p,p'*-DDE was lipid-adjusted by

regression methods (Dello Iacovo et al. 1999; Hunter et al. 1997; Moysich et al. 1998). All the statistical analyses were performed using the software Stata release 7.0 (Stata Corp., College Station, TX, USA).

Results

Tables 1, 2 and 3 describe the 22 studies that were included in the meta-analysis. All were case-control studies, and of these nine were prospective (nested case-control) (Dorgan et al. 1999; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; Wolff et al. 1993, 2000b) and 13 retrospective (Aronson et al. 2000; Dello Iacovo et al. 1999; Demers et al. 2000; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Stellman et al. 2000; van't Veer et al. 1997; Wolff et al. 2000a; Zheng et al. 1999, 2000). Among the retrospective studies, four were population-based case-control studies (Dello Iacovo et al. 1999; Millikan et al. 2000; Moysich et al. 1998; van't Veer et al. 1997) and seven were clinic-based case-control studies (Aronson et al. 2000; López-Carrillo et al. 1997; Mendonca et al. 1999; Stellman et al. 2000; Wolff et al. 2000a; Zheng et al. 1999, 2000); in one study only a subsample of a population-based case-control study population was analyzed (Romieu et al. 2000); and another study included two types of controls: population and clinical (Demers et al. 2000). All the studies are presented in the tables according to decreasing date of publication and design features.

Thirteen studies were conducted in the United States (Dorgan et al. 1999; Helzlsouer et al. 1999; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; Millikan et al. 2000; Moysich et al. 1998; Stellman et al. 2000; Wolff et al. 1993, 2000a, 2000b;

Zheng et al. 1999, 2000), two in Canada (Aronson et al. 2000; Demers et al. 2000), two in Denmark (Hoyer et al. 1998, 2000b), two in Mexico (López-Carrillo et al. 1997; Romieu et al. 2000), one in Italy (Dello Iacovo et al. 1999), one in Germany, Netherlands, Ireland, Switzerland, Spain (van't Veer et al. 1997), and one more in Brazil (Mendonca et al. 1999). The number of cases ranged from 58 in the study performed by Wolff et al. (1993) to 456 in the study performed by Millikan et al. (2000).

The inclusion criteria of the referent groups varied among studies. Individuals with skin cancer were accepted in the control group by some studies, (Dorgan et al. 1999; Helzlsouer et al. 1999; Wolff et al. 2000a) whereas in others controls had been diagnosed with benign breast disease (Aronson et al. 2000; Stellman et al. 2000; Wolff et al. 2000a), and in the remaining studies only healthy individuals and/or subjects with no cancer diagnosis made up the comparison group (Dello Iacovo et al. 1999; Demers et al. 2000; Hoyer et al. 1998, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; van't Veer et al. 1997; Wolff et al. 1993, 2000b).

In most studies, body burden levels of *p,p'*-DDE were measured in serum samples (Dello Iacovo et al. 1999; Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Wolff et al. 1993, 2000a, 2000b; Zheng et al. 2000), but in four studies, adipose tissue from the breast (Aronson et al. 2000; Stellman et al. 2000; Zheng et al. 1999)

Table 2. Retrospective epidemiologic population-based case-control studies on *p,p'*-DDE and breast cancer risk.

Reference, location	Cases/controls (n)	Controls	Biologic specimen	Controlled variables ^a			<i>p,p'</i> -DDE ORs (95% CI)	
				Age	Reproductive variables	History of breast cancer		Other variables
Millikan et al. 2000 North Carolina, USA	456/389	Free of disease	Serum	X	X	X	X ^b	High vs. low tertile 1.09 (0.79–1.51)
Demers et al. 2000 Québec, Canada	315/307	Free of disease	Serum	X	X	X	X ^c	High vs. low quintile 1.00 (0.60–1.67)
Romieu et al. 2000 Mexico City, Mexico	120/126	Free of disease (subsample)	Serum	X	X	X	X ^d	High vs. low quartile 3.81 (1.14–12.80) <i>p</i> for trend = 0.02
Dello Iacovo et al. 1999 Naples, Italy	170/190	Free of disease	Serum	X	X	—	X ^e	High vs. low tertile 1.24 (0.70–2.20)
Moysich et al. 1998 Western New York State, USA	154/192	Free of disease	Serum	X	X	X	X ^f	High vs. low tertile 1.34 (0.71–2.55)
van't Veer et al. 1997 Germany, Netherlands, Northern Ireland, Switzerland, Spain	265/341	Free of disease	Buttocks Adipose tissue	X	X Except breast-feeding	—	X ^{g,h}	High vs. low quartile 0.48 (0.25–0.95) <i>p</i> for trend = 0.02

BMI, body mass index.

^aIn design or analysis. ^bHormone replacement treatment, income and race, BMI, age. ^cRegion of residence and history of benign breast disease, BMI. ^dDDT serum levels, BMI, socioeconomic status. ^eBMI, cholesterol. ^fFruit and vegetable intake, lipid serum, education, and BMI. ^gHospital controls and population controls were used together. ^hAlcohol consumption, study site, and BMI.

or the buttocks (van't Veer et al. 1997) were the biologic matrices chosen to estimate the cumulative exposure to p,p' -DDE. The collection of biologic specimens dated back to about 10–25 years before the diagnosis of breast cancer in the prospective case–control studies (Dorgan et al. 1999; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; Wolff 1993, 2000b) to the period immediately around the date of diagnosis in all retrospective studies (Aronson et al. 2000; Dello Iacovo et al. 1999; Demers et al. 2000; López-Carrillo et al. 1997, Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Stellman et al. 2000; van't Veer et al. 1997; Wolff et al. 2000a; Zheng et al. 1999, 2000).

The results of all studies were controlled by the age of the participants. The control of other potential confounders, either in the design or the analysis, was distinct across the studies. History of breast-feeding was not considered in six studies (Dorgan et al. 1999; Hoyer et al. 1998, 2000b; Krieger et al. 1994; Stellman et al. 2000; van't Veer et al. 1997), and parity and menopausal status were controlled in most studies but not in two (Dorgan et al. 1999; Stellman et al. 2000). History of familial breast cancer and/or benign breast disease was controlled in most of the studies (Aronson et al. 2000; Demers et al. 2000;

Helzlsouer 1999; Hunter 1997; Laden et al. 2001b; López Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Wolff et al. 1993, 2000a, 2000b; Zheng et al. 2000) as well as body mass index (Aronson et al. 2000; Dello Iacovo et al. 1999; Demers et al. 2000; Helzlsouer et al. 1999; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; López-Carrillo et al. 1997; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Stellman et al. 2000; van't Veer et al. 1997; Wolff et al. 2000b; Zheng et al. 1999, 2000). Other adjustment variables were fasting status (Hunter et al. 1997; Laden et al. 2001b), day of menstrual cycle at the date of blood sampling (Helzlsouer et al. 1999; Wolff et al. 1993, 2000b), vital and/or income status (Hoyer et al. 1998, 2000b; Millikan et al. 2000; Zheng et al. 1999, 2000), physical activity (Hoyer et al. 1998), use of hormonal replacement therapy (Aronson et al. 2000; Laden et al. 2001b; Millikan et al. 2000; Hunter et al. 1997; Zheng et al. 2000), tobacco smoking (Aronson et al. 2000; Hoyer et al. 1998; Mendonca et al. 1999), and alcohol consumption (Aronson 2000; Hoyer et al. 1998; van't Veer et al. 1997) as well as intake of fruits, vegetables (Moysich et al. 1998), and fat (Aronson et al. 2000; Zheng et al. 2000).

Overall, the data provided by the published studies do not support an association

between p,p' -DDE body burden levels and breast cancer risk, because the summary OR was 0.97 (95% CI, 0.87–1.09) (Figure 1). We found no evidence for significant overall heterogeneity in the OR [$\chi^2 = 27.93$; degrees of freedom (df) = 23; $p = 0.218$].

Summary ORs for prospective and retrospective population-based case–control and retrospective hospital-based case–control studies were 0.91 (95% CI, 0.74–1.12), 1.11 (95% CI, 0.89–1.38), and 0.93 (95% CI, 0.77–1.12), respectively (Figure 2). Although summary ORs did not show significant heterogeneity within prospective or retrospective hospital-based case–control studies ($\chi^2 = 10.68$; df = 9; $p = 0.298$, and $\chi^2 = 4.107$; df = 7; $p = 0.767$, respectively), we found a borderline statistically significant test of heterogeneity within retrospective population-based case–control studies ($\chi^2 = 11.23$; df = 5; $p = 0.047$) in the study performed by van't Veer et al. (1997).

Summary ORs were not different for the 16 studies where breast-feeding was controlled as confounder (Aronson et al. 2000; Dello Iacovo et al. 1999; Demers et al. 2000; Helzlsouer et al. 1999; Hunter et al. 1997; Laden et al. 2001b; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Wolff et al. 1993, 2000a, 2000b; Zheng et al.

Table 3. Retrospective epidemiologic (hospital-based case–control) studies on p,p' -DDE and breast cancer risk.

Reference, location	Cases/controls (n)	Controls	Biologic specimen	Controlled variables ^a				p,p' -DDE ORs (95% CI)
				Age	Reproductive variables	History of breast cancer	Other variables	
Stellman et al. 2000 New York State, USA	232/323	Benign breast disease and surgical-nonbreast diseases	Breast adipose tissue	X	—	—	X ^b	High vs. low tertile 0.74 (0.44–1.25)
Demers et al. 2000 Québec, Canada	315/219	Free of gynecologic diseases	Serum	X	X	X	X ^c	High vs. low quintile 1.36 (0.71–2.63)
Aronson et al. 2000 Ontario, Canada	217/213	Benign breast disease	Breast adipose tissue	X	X	X	X ^d	High vs. low quartile 1.62 (0.84–3.11)
Wolff et al. 2000a New York City, USA	175/181/175	Benign breast disease except BBD with hyperplasia or atypia and non-benign disease and free of cancer except skin cancer	Serum	X	X	X	X ^e	High vs. low tertile 0.93 (0.56–1.5)
Zheng et al. 1999 Connecticut, USA	304/186	Benign breast disease except atypical hyperplasia and normal breast tissue	Breast adipose tissue	X	X	—	X ^f	High vs. low quartile 0.9 (0.5–1.5)
Zheng et al. 2000 Connecticut, USA	326/347	Benign breast disease except atypical hyperplasia and normal breast tissue	Serum	X	X	X	X ^g	High vs. low quartile 0.96 (0.67–1.36)
Mendonca et al. 1999 Rio de Janeiro, Brazil	177/350	Free of disease (hospital visitor)	Serum	X	X	X	X ^h	High vs low quintile 0.83 (0.4–1.6)
López-Carrillo et al. 1997 Mexico City, Mexico	139/139	Free of cancer or any other breast disease	Serum	X	X	X	X ⁱ	High vs. low tertile (0.41–1.42)

BMI, body mass index.

^aIn design or analysis. ^bHospital, BMI, race. ^cRegion of residence and history of benign breast disease, BMI. ^dStudy site, present use of hormonal replacement therapy, BMI, fat intake, race, alcohol intake, smoking. ^eRace, BMI, age. ^fIncome 10 years before the disease diagnosis or interview, BMI, race. ^gBMI, lifetime months of hormone replacement therapy, dietary fat intake, race, and study site. ^hTobacco smoking and breast size, educational level. ⁱBMI.

1999, 2000) and the estimate was 1.01 (95% CI, 0.88–1.16), compared to the OR for studies in which breast-feeding was uncontrolled (OR = 0.87; 95% CI, 0.68–1.10) (Dorgan et al. 1999; Hoyer et al. 1998, 2000b; Krieger et al. 1994; Stellman et al. 2000; van't Veer et al. 1997). There were no differences either for the 18 studies using blood serum as biologic specimen 1.00 (95% CI, 0.88–1.14) (Dello Iacovo et al. 1999; Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Hoyer et al. 1998, 2000b; Hunter et al. 1997; Krieger et al. 1994; Laden et al. 2001b; López-Carrillo et al. 1997; Mendonca et al. 1999; Millikan et al. 2000; Moysich et al. 1998; Romieu et al. 2000; Wolff et al. 1993, 2000a, 2000b; Zheng et al. 2000) or for studies that used adipose tissue 0.84 (95% CI, 0.62–1.13) (Aronson et al. 2000; Stellman et al. 2000; Zheng et al. 1999; van't Veer et al. 1997) (Table 4). No evidence of publication bias was found ($p = 0.253$).

In Figure 3 we depict a significantly decreasing trend ($\beta = -130.59$; $p = 0.001$) of the mean levels of p,p' -DDE that were evaluated by the studies analyzed, according to the

date when the biologic sample was collected. All those levels were converted to the corresponding equivalent nanograms per gram in lipid serum bases. Significantly, p,p' -DDE levels as reported by the study carried out in Mexico City by Romieu et al. (2000), were at great variation with the other studies performed at about the same time, including the one performed in that same city (López-Carrillo et al. 1997).

In Figure 4 we present the ORs for the effect of p,p' -DDE on breast cancer risk from each study, according to the gradient of the p,p' -DDE body burden levels expressed as nanograms per gram in serum lipid bases (middle point of p,p' -DDE levels for each category of exposure). The range of that gradient varied from 84.37 ng/g in the study performed by Mendonca et al. (1999), to 12928.08 ng/g in the study by Krieger et al. (1994). As shown in Figure 4, most studies reported p,p' -DDE body burden levels in the range of 84.37–9,000 ng/g and yielded negative results, with two exceptions (Romieu et al. 2000; Wolff et al. 1993). The studies that had the highest levels of p,p' -DDE body burden

levels (9,001–12928.08 ng/g) did not show an increasing risk of breast cancer due to p,p' -DDE body burden levels (Dorgan et al. 1999; Krieger et al. 1994; van't Veer et al. 1997).

Discussion

The results of the meta-analysis of 22 studies showed no evidence for an association between p,p' -DDE body burden levels and breast cancer risk. The summary OR reported in this manuscript was 0.97 (95% CI, 0.87–1.09), very similar to the one recently estimated from a pooled analysis of five studies (OR = 0.99; 95% CI 0.77–1.27) performed in the United States (Laden et al. 2001a) and had the same covariates to be included in the logistic models. Some studies (Hunter 1997, Laden 2001a, Wolff 1993, 2000b) apparently made repeated use of some subjects as part of their study populations in subsequent papers. Hence, one additional check was to remove in subsequent steps those studies for which we believed that such condition could be met, and the estimates of summary ORs remained almost unaltered (data not shown).

An intrinsic flaw in many environmental epidemiologic studies is the lack of an adequate gradient of exposure both within and throughout the different populations studied. On average, the difference between the highest and the lowest levels of p,p' -DDE in the 22 studies was 6928.92 ± 6414.5 ng/g. The studies that had the widest internal gradient of exposure were negative (Dorgan et al. 1999; Krieger et al. 1994) as were the studies that reported the highest levels of p,p' -DDE. (Dorgan et al. 1999; Krieger et al. 1994). In this regard, evidence from occupational studies, which evaluated much higher levels of p,p' -DDE exposure, does not suggest a high risk for breast cancer (Austin et al. 1989; Fleming et al. 1999). Hence, we believe we can rule out the possibility that contradictory results among the 22 studies are caused by differences in p,p' -DDE levels.

Methodologic features among the studies that may explain the contradictory results include differences in the temporal relationship between the measurement of p,p' -DDE

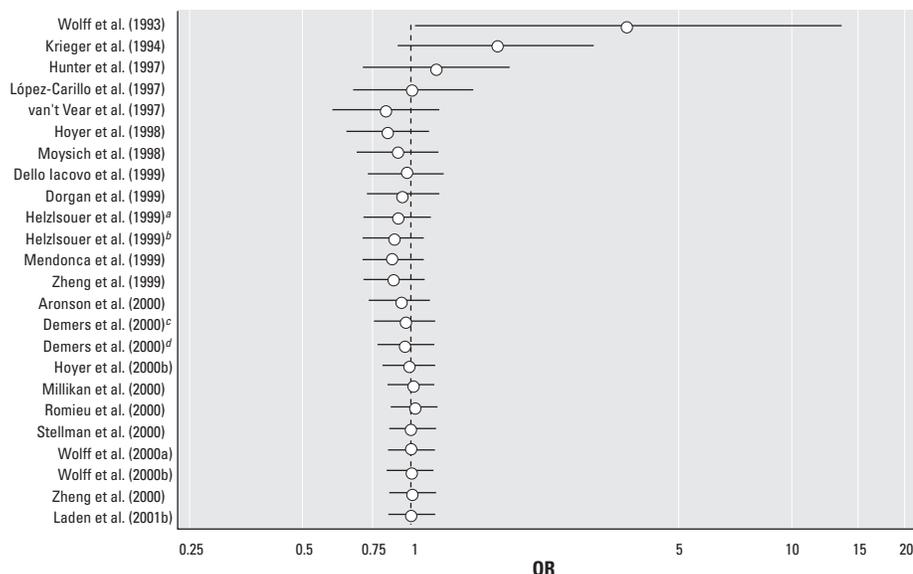


Figure 1. Accumulated meta-analysis; summary OR = 0.97 (95% CI, 0.87–1.09).

^aBiologic samples taken in 1974. ^bBiologic samples taken in 1989. ^cControls are population based. ^dControls are clinical based.

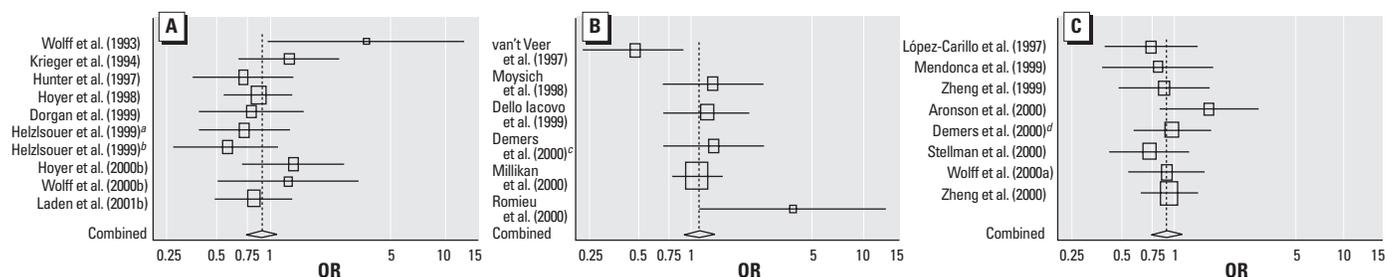


Figure 2. Meta-analysis according to type of design: (A) prospective studies (nested case-control); (B) retrospective studies (population-based case-control); (C) retrospective studies (hospital-based case-control).

^aBiologic samples taken in 1974. ^bBiologic samples taken in 1989. ^cControls are population based. ^dControls are clinical based.

levels and the diagnosis of breast cancer. Levels of *p,p'*-DDE that are measured around the date of diagnosis may not reflect the real exposure at disease onset. However in this article we showed that the association between *p,p'*-DDE and breast cancer risk did not vary

according to the type of the study (i.e., prospective case-control studies vs. retrospective case-control studies), and this information should be interpreted as evidence that temporality does not explain different results among the studies.

Table 4. Overall ORs for breast cancer risk and *p,p'*-DDE body burden levels.

Studies included in the analysis	No of studies ^a	OR (95% CI)
All	22	0.97 (0.87–1.09)
Prospective nested case-control	9	0.91 (0.74–1.12)
Retrospective case-control		
Population based	6	1.11 (0.89–1.38)
Hospital based	7	0.93 (0.77–1.12)
Breast-feeding control		
Yes	16	1.01 (0.88–1.16)
No	6	0.87 (0.68–1.10)
<i>p,p'</i> -DDE levels		
Serum	18	1.00 (0.88–1.14)
Adipose tissue	4	0.84 (0.62–1.13)

^aIn total, 22 studies were useful for the purposes of this table; Demers et al. (2000) contributed data for clinical and population controls, which were considered separately. That was also the case for Helzlsouer et al. (1999), in which serum samples were reported for two different moments in time: 1974 and 1989. Thus the sample size for the analysis became 24.

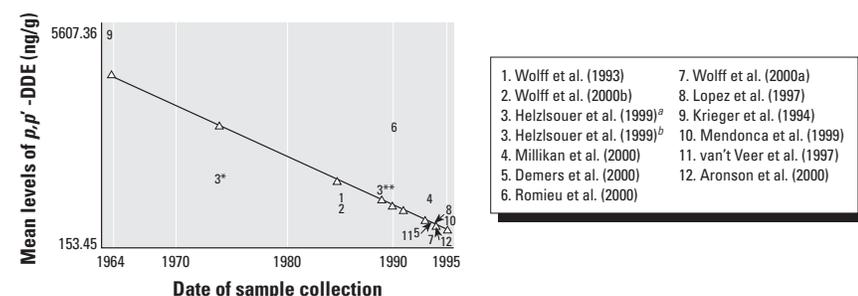


Figure 3. Mean levels of *p,p'*-DDE (ng/g) in 12 reported studies according to the date of sample collection. Δ , fitted values.

^aBiologic samples taken in 1974. ^bBiologic samples taken in 1989.

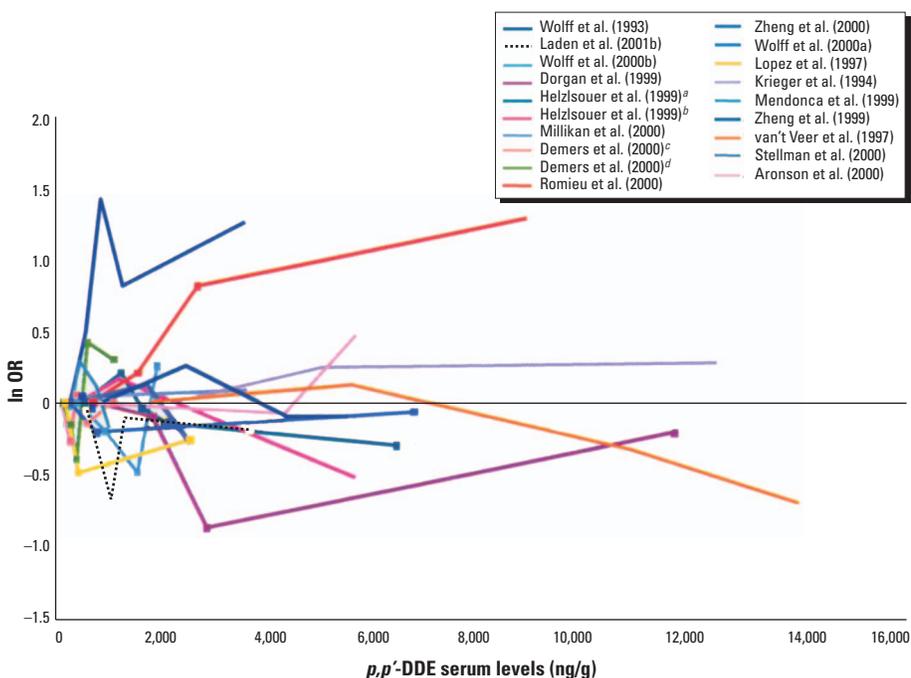


Figure 4. Effect of *p,p'*-DDE on breast cancer risk from each study according to *p,p'*-DDE (ng/g) body burden levels. ln, natural logarithm.

^aBiologic samples taken in 1974. ^bBiologic samples taken in 1989. ^cControls are population based. ^dControls are clinical based.

Confounding is a potential explanation for inconsistent epidemiologic results. Among the confounders that might distort the relationship between *p,p'*-DDE and breast cancer risk are breast-feeding and diet. Lactation is a way of eliminating the body burden levels of *p,p'*-DDE (López-Carrillo et al. 2001) and has been found to decrease the risk of breast cancer in several studies (Romieu et al. 1996). However, we found no heterogeneity in our meta-analysis to assign explanatory relevance to the lack of control by this variable in some of the published studies. Yet this analysis is not enough to rule out the possibility that equivocal results might be partially explained by differences in the ranges of values for the adjustment variables across the studies; moreover, measurement error in the confounding variables is likely to result in unpredictably biased estimates of effect for the main variable of interest when adjustments are performed.

Residues of *p,p'*-DDE were reportedly found in several foods (fish, dairy products, meat) (Galván-Portillo et al. 2002), and the consumption of some of them may be related to breast cancer risk. For example, meat intake is related to an excess risk for breast cancer, whereas fish intake, presumably because of the presence of omega-3 fatty acids, seems to be inversely related to breast cancer incidence (World Cancer Research Fund 1997). A study performed by Verma et al. (1997) showed that genistein, an isoflavonoid present in soybeans, and curcumin, a component of turmeric powder and also a widely used spice, can inhibit the action of pesticides with estrogenic activity. The great variation in breast cancer risk raises the possibility that dietary factors are related to its etiology. In this regard, dietary factors and particularly specific compounds such as phytoestrogen were scarcely or not at all taken into account as covariates in studies of *p,p'*-DDE and breast cancer risk; thus, the lack of adjustment by these variables might partially explain the equivocal results so far available.

Another methodologic issue of concern is the type of controls that were enrolled—i.e., hospital or population based—in that one should expect that *p,p'*-DDE body burden levels were not related to the diseases identified among clinical controls, and also that population controls actually constitute a representative sample of the *p,p'*-DDE body burden levels present in the target population (Rothman and Greenland 1998). We were not able to find heterogeneity according to the study design, except for a borderline significant result within retrospective population-based case-control studies ($\chi^2 = 11.23$; $df = 5$; $p = 0.047$). And this variation mainly arose from the study by van't Veer et al. (1997), which assembled a referent group that combined hospital- and population-based controls and provided no explanation for such an unusual combination.

Consistent with the prohibition against DDT, which took place between 1972 and 1997 in many countries, a decreasing trend in *p,p'*-DDE levels is observed when considering the year of biologic sample collection, with one exception (Romieu et al. 2000), a study that reported *p,p'*-DDE levels about 5-fold higher than the ones previously observed in the same area and a similar study population (López-Carrillo et al. 1997).

The two Mexican studies were performed among residents of Mexico City, where DDT has never been used, although this substance was still in use until 1997 for vector control in the tropical areas of the country. One may speculate that the route of exposure to *p,p'*-DDE for residents of Mexico City was the ingestion of contaminated foods brought from areas where DDT was being sprayed (Torres-Arreola et al. 1999). Nevertheless, body-burden levels should not be appreciably different between the two studies or from those observed in other urban areas of the world [levels of exposure reported by López-Carrillo et al. (1997)]. To strengthen this point, a reproducibility study was performed between a U.S. laboratory and the laboratory that processed the samples of the first Mexican study (see also Torres-Arreola 2002). The results showed a very high correlation coefficient (0.985), and the mean values of *p,p'*-DDE for 10 spiked serum samples were 21.47 ± 7.09 and 19.24 ± 7.20 , respectively (Torres-Arreola et al. 2002). Regrettably, no similar information is available for the study by Romieu et al. (2000) to exclude a systematic error that could explain the unexpectedly high levels of *p,p'*-DDE they reported.

In the context of the measurement of exposure, we found no evidence that the type of biologic specimen used to measure *p,p'*-DDE levels was related to the conflicting results stemming from the published studies. Moreover, in a previous study our research group demonstrated that the relationship between *p,p'*-DDE levels in serum and adipose tissue is close to unity when the results are normalized and adjusted by lipid content (López-Carrillo et al. 1999), and that finding is consistent with the lack of heterogeneity herein reported.

The lack of a positive association between *p,p'*-DDE body burden levels and breast cancer risk could be explained by the low estrogenicity of *p,p'*-DDE, compared with the less persistent metabolites of technical DDT, which are *p,p'*-DDT and *o,p'*-DDT. *In vivo* tests showed no increase in wet uterine weight gain in immature or ovariectomized rodents and a weak binding of estradiol to rodent uterine receptors or to any form of human estrogen receptors in relation to *p,p'*-DDE. Since the 1970s, the major route of exposure to DDT has been the far less estrogenic

p,p'-DDE contained in the diet, and not the more estrogenic *o,p'*-DDT found in technical DDT, which was sprayed as an insecticide (Snedeker 2001). In this context, the significant association with breast cancer at relatively low levels of exposure to *p,p'*-DDE reported by Wolff et al. in 1993 might be a chance finding (i.e. a type I error).

Some aspects are not yet accounted for in the studies performed so far. The exposure to DDT during the critical periods of development—from conception through adolescence—may be related to adult breast cancer; however, individual variations in metabolizing enzymes of DDT and its derivatives are likely to modify the consequences of the exposure to this compound, and certainly that is an incipient area for health research. Nevertheless, we believe that the results of this meta-analysis should be regarded as strong evidence against the putative association between DDT and breast cancer risk.

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